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EXAMINER	
KIM, YOUNG J	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 11/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/816,763	REMACLE ET AL.	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-8,12-22,34,36 and 37* is/are pending in the application.

4a) Of the above claim(s) *19-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-8,12-18,22,34,36 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The present Office Action is responsive to the Amendment received on July 8, 2005.

Preliminary Remark

Petition for the withdrawal of the holding of abandonment, made on August 1, 2005 had been granted.

Claims 3, 9-11, 23-33, 35, and 38 are canceled.

Claims 1, 2, 4-8, 12-22, 34, 36, and 37 are pending and are under prosecution herein.

Priority

The examiner agrees with Applicants' statement regarding the foreign application to which Applicants claim priority under 35 U.S.C. 119(a)-(d) – that is, the document is in English.

However, the priority cannot be granted because Applicants have not filed a certified copy of the foreign document to which Applicants claim foreign priority as required by 35 U.S.C. 119(b).

Applicants are invited to submit such a document or submit evidence that such was filed when the instant application was filed.

Claim Objections

The objection of claims 1, 2, 4-8, 12-15, 17, 18, 22, 34, 36, and 37 for minor grammatical issues, made in the Office Action mailed on January 7, 2005 is withdrawn in view of the Amendment received on July 8, 2005.

The objection of claims 1, 2, 4-8, 12-18, 22, 34, 36, and 37 for containing a period after each sub-step, made in the Office Action mailed on January 7, 2005 is withdrawn in view of the Amendment received on July 8, 2005.

The objection of claims 19-21 made in the Office Action mailed on January 7, 2005 is maintained.

Claims 19-21 are objected to because the claims are drawn to a separate invention, which cannot be practiced together with the elected invention.

Claim 1, to which the above claims depend from, is drawn to a method which comprises the step of binding transcriptional factors to immobilized double-stranded DNAs.

Claim 19 is drawn to a method for screening, quantifying and/or recovering ***compounds*** that modulate the activity of the transcriptional factors when put in cells. The claim requires the administration of compounds in cells, in order to identify which compounds modulate the activity of the transcription factors, thus not requiring the DNA array nor can the methods be practiced together.

Claim 20 is drawn to a method for screening, quantifying and/or recovering ***compounds*** which modulate the activity of enzymes or proteins acting on transcriptional factors which are then further assay for their binding to the transcriptional factors. This method also, cannot be practiced together with claim 1 which requires the use of a DNA array.

Claim 21 is drawn to a method drawn to identification of transcriptional factors and/or peptides which are part of their active complex. This method also cannot be practiced together with the method of claim 1.

Claims 19-21 have not been further treated on their merits.

While Applicants contend that the claims had been amended to become drawn to a method of the elected invention, it is respectfully submitted that claims 19-21 are drawn to a method of screening for modulators of transcriptional factors. Such method is distinct from the elected

invention which is drawn to a method of screening for DNA molecules which bind transcriptional factors.

Claims are not further treated on their merits therefore.

Claim Rejections - 35 USC § 112

The rejection of claims 1, 2, 4-8, 12-18, 22, 34, 36, and 37 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter, made in the Office Action mailed on January 7, 2005 is withdrawn in view of the Amendment received on July 8, 2005.

Claim Rejections - 35 USC § 103 - Maintained

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 1, 2, 4-8, 12-18, 22, 36, and 37 under 35 U.S.C. 103(a) as being unpatentable over Peterson et al. (U.S. Patent No. 5,563,036, issued October 8, 1996) in view of Heslot et al. (U.S. Patent No. 6,342,353 B1, issued January 29, 2002, 102(e) date November 4, 1999) and Nerenberg et al. (US 2002/0015198 A1, published August 22, 2002, filed September 20, 2001, priority September 20, 2000), made in the Office Action mailed on January 7, 2005 is maintained for the reasons of record.

Applicants' arguments presented in the Amendment received on July 8, 2005 have been fully considered in view the Declaration received on October 12, 2004, but they are not found persuasive for the reasons set forth in the, "Response to Arguments" section.

The Rejection:

Peterson et al. disclose a method comprising the steps of: a) binding to a solid substrate (thus insoluble), such as microtiter plate (column 5, line 34-36; column 7, line 23; column 8, lines 59-60), double-stranded DNA sequences (column 6, lines 26-28), at the concentration greater than 0.01 pmoles/cm^2 (column 10, line 26), wherein said double-stranded DNA is connected to the surface of the solid support via avidin-biotin binding (column 7, lines 13-18) or antigen/antibody binding (column 7, lines 18-19); b) contacting transcriptional factors with said solid-surface bound double-stranded DNAs (column 3, lines 1-5; column 4, lines 37-41); and c) identifying and/or quantifying a signal resulting from the binding of the transcriptional factors to said solid-surface bound double-stranded DNAs (column 8, lines 64-68).

Peterson et al. do not teach that the double-stranded DNAs is connected to the surface of the solid-surface support by *a spacer* comprising at least a *double-stranded* DNA nucleotide sequence of between about 50 and about 250 base pairs.

Peterson et al. do not explicitly teach that the solid-support be an array bearing at least 4 spots/cm^2 of solid support surface.

Peterson et al., while explicitly disclosing that their method involves transcriptional factors that may be derived from, "a host or from ***an infectious or parasitic organisms***" (column 3, lines 9-13), as well as HIV TAT (Table 1, column 5, lines 21-25), do not explicitly disclose that the transcriptional factor be HIV Integrase.

Heslot et al. disclose a method involving the immobilization of double-stranded DNA (column 1, lines 9-10) via a spacer arm which is also double-stranded DNA (column 4, lines 36-37), wherein said spacer arm comprises the length of 5 to 1kb in length (column 4, lines 39-40), for the explicit purpose of providing "freedom of movement." (column 4, lines 16-17).

Nerenberg et al. disclose a well-known use of sensor array comprising high-density array of immobilized nucleic acids, wherein artisans ***explicitly*** disclose that the sensor array of the invention would be useful in screening in "a solution analytes that might be transcriptional factors such as activators or repressors." [0134]. Nerenberg et al. also explicitly disclose that nucleic acid binding to integrase is measured in their sensor [0134].

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Peterson et al. with that of Heslot et al. and Nerenberg et al. to arrive at the invention as claimed for the following reasons.

The use of spacer arms in an array technology for the purpose of providing freedom to immobilized ligands have been known and established in the art. Previously cited Saiki et al. document as well as the disclosure of Heslot et al. supports such knowledge.

Therefore, one of ordinary skill in the art at the time the invention was made would have been easily motivated to modify the teachings of Peterson et al. with the use of any spacer arm for the advantage of providing freedom to immobilized ligands. One of ordinary skill in the art at the time the invention was made also would have had a clear expectation of success at using a double-stranded DNA spacer arm in conjunction with the method of Peterson et al. because Heslot et al. explicitly demonstrated that such combination would work, as well as disclosing that either double-stranded or other known polymers would work as effectively (column 4, lines 40-45).

MPEP, at 2143.02 states that the prior art can be modified or combined to reject claims as obvious as long as there is a reasonable expectation of success. As already discussed above, one of ordinary skill in the art would have had a clear expectation of success at using a double-stranded DNA spacer arm in combination with the method disclosed by Peterson et al. as the use of such technologies has been well-known, enabled, and established in the art.

With regard to the density limitation of the solid support being an array comprising at least 4 spots per cm^2, the advantage of using a high-density microarray has been well-established in the art as allowing multiple reactions in a miniaturized area, and whether the surface comprise at least 4 spots or any number of spots would be well-within the purview of an ordinarily skilled artisan in the art of array technology.

Therefore, for the above reasons, claims 1, 6, 8, 12-17, 22, 36, and 37 are obvious over the cited references.

With regard to claim 2, Peterson et al. disclose the transcriptional factor being present at a concentration lower than 20 nM (column 10, lines 40-41).

With regard to the labeling being non-radioactive (instant claim 4) or obtained through enzymatic reactions (instant claim 5), Peterson et al. disclose that the labeling could be luminescence (or non-radioactive), or indirect detection such as epitope tag, an enzyme (column 6, lines 13-17).

With regard to the transcription factors being selected from those recited in the Markush group of claim 7, Peterson et al. disclose a plurality of the recited transcriptional factors in their Table 1 (beginning at column 3, line 30 through column 5).

With regard to screening for compounds that modulate the binding of transcriptional factors (instant claim 18), Peterson et al. disclose that the mixture applied as a sample comprises candidate

pharmacological compounds that comprise functional chemical groups necessary for structural interactions with proteins and/or DNA (column 5, line 35; column 7, lines 28-46).

Therefore, for the above reasons, the invention as claimed is *prima facie* obvious over the cited references.

Response to Arguments:

Applicants' point of contention is that Peterson et al. do not suggest or mention the use of a spacer between about 50 and about 250 bp recited in the independent claim 1 (page 8, 1st paragraph, Response). Applicants rely on their Declaration so as to attempt to demonstrate that the use of spacers between 50 and about 250 bp in length provides enhanced signal levels relative to the levels observed when the binding site is separated from the support by shorter sequences with a length similar to those described in Peterson (page 8, 1st paragraph, Response).

Applicants refer to Declaration in their attempt to demonstrate that the increasing spacer lengths increased signal intensities for some of the transcription factors which claimed in the instant application (page 8, 3rd paragraph, Response).

Applicants emphasizes the importance of optimal spacer size for providing advantages in detecting and quantifying transcription factor binding (page 9, 1st paragraph, Response).

While Applicants' arguments have been considered carefully, the arguments are not found persuasive for the following reasons.

According to column 6, beginning at line 26, Peterson et al. discuss the below:

Clearly, Peterson et al. state that the double-stranded DNA molecule which binds the transcriptional factor

> The nucleic acid conjugate comprises a nucleic acid coupled to a ligand. The nucleic acid is usually linear and double-stranded DNA or RNA, particularly in the case of retroviral transcription factor binding sites, though circular plasmids or other nucleic acids or structural analogs may be substituted so long as transcription factor sequence-specific binding is retained. In some applications, supercoiled DNA provides optimal sequence-specific binding and is preferred. The nucleic acid may be of any length amenable to the assay conditions and requirements. Typically the nucleic acid is between 8 bp and 5 kb, preferably between about 12 bp and 1 kb, more preferably between about 18 bp and 250 bp, most preferably between about 27 and 50 bp.
>
> The nucleic acid has a sequence at least a portion of which is common to the gene or gene regulatory region to which the native transcription factor normally binds. The portion may be continuous or segmented and shares sufficient sequence and sequence similarity with the gene or gene regulatory region to provide sequence-specific binding of the labelled protein. Typically, this binding site portion of the nucleic acid constitutes at least about 4, preferably at

ranges from 18 bp to 250 bp (at line 38). Not only do Peterson et al. state this fact, but the artisans also clearly state only a portion of the nucleic acid must comprise gene or gene regulatory region to which the native transcription factors bind (at lines 39-41).

Based on such a disclosure, one of ordinary skill in the art would have clearly recognized that out of at least 250 bp of DNA molecule, only a portion of such molecule need comprise a region to which the transcription factors bind, leaving the rest of the double stranded region.

The instant claims only define a spacer as that which is double-stranded, having the length of about 50 to about 250. In this respect, such a remaining region disclosed by Peterson could be considered to be a double stranded "spacer" molecule.

In addition, the Examiner respectfully disagrees with the Applicants' position that the determination of spacer length is an inventive discovery.

The use of a spacer molecule in a microarrays have long been established, for the well-known advantage of providing freedom of movement for the immobilized oligonucleotides to bind to their targets. Such spacers ranges from polydT to repeating polyethylene glycol units, so as to displace the oligonucleotide probes from the solid surface and provide freedom of movement.

Hence, one of ordinary skill in the art would have been clearly motivated to employ a spacer molecule for the molecules of Peterson et al. for the same benefit of displacing the DNA molecules from the solid surface, resulting in the greater freedom of the molecules for binding the target (i.e., easily accessible). Just as the use of spacer molecules provides facilitated and increased efficiency in hybridization (in a microarray assay), one of ordinary skill in the art would have had a clear expectation, or at minimum, had a reasonable expectation that the same benefit would have been achieved in the method of Peterson et al.

Lastly, given the motivation to employ a spacer molecule in the teachings of Peterson et al., the determination of the optimal length for the spacer molecule would have only required routine experimentation, involving routine optimization of known conditions.

Given the fact that Heslot et al. demonstrate the feasibility of immobilizing double-stranded nucleic acids on a solid surface, one of ordinary skill in the art at the time the invention was made would have had no doubt that producing such combination of teachings would have worked.

While Applicants state that a spacer of a specific length will allow firstly the improvement of detection of some specific transcriptional factors and contends that such observance was not resulting from a "possible freedom of movements" of the bound double-stranded DNA sequences, but from the binding characteristics of the transcriptional factors (page 9, bottom paragraph, Response), this statement is not found convincing because Declaration clearly shows that the binding efficiency clearly increased with the increase in the length of the spacer molecule being employed (referring to Exhibit 2).

Therefore, the rejection is maintained for the reasons of record.

The rejection of claim 34 under 35 U.S.C. 103(a) as being unpatentable over Peterson et al. (U.S. Patent No. 5,563,036, issued October 8, 1996) in view of Heslot et al. (U.S. Patent No. 6,342,353 B1, issued January 29, 2002, 102(e) date November 4, 1999) and Nerenberg et al. (US 2002/0015198 A1, published August 22, 2002, filed September 20, 2001, priority September 20, 2000) as applied to claims 1, 2, 6-8, 12-18, 22, 36, and 37 above, and further in view of Dattagupta et al. (U.S. Patent No. 4,968,602, issued November 6, 1990), made in the Office Action mailed on January 7, 2005 is maintained for the reasons of record.

Applicants' arguments presented in the Amendment received on July 8, 2005 have been fully considered but they are not found persuasive for the reasons set forth in the, "Response to Arguments" section.

The Rejection:

The teachings of Peterson et al., Heslot et al., and Nerenberg et al. have been already discussed above.

While Peterson et al. explicitly disclose that avidin/biotin binding could be employed for immobilizing double-stranded DNA, none of the artisans explicitly disclose that streptavidin, in place of avidin could be employed.

Dattagupta et al. explicitly state that biotin can be coupled to either ***avidin or streptavidin*** (column 18, lines 32-37).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the avidin with streptavidin of Dattagupta et al. to arrive at the claimed method involving streptavidin/biotin binding for the following reaons.

MPEP, at 2143.02, states that the prior art can be modified or combined to reject claims as ***prima facie*** obvious as long as there is a reasonable expectation of success. Given that the use of avidin or streptavidin for its binding with biotin for the purpose of immobilizing nucleic acids have been well-established in the art as established by the date of the patent of Dattagupta et al. as well as their explicit teaching, one of ordinary skill in the art at the time the invention was made would have had a clear expectation of success at modifying the teachings of Peterson et al., Heslot et al., and Nerenberg et al. to arrive at the invention as claimed.

Therefore, for the above reasons, the invention as claimed is *prima facie* obvious over the cited references.

Response to Arguments:

Applicants do not present any new arguments for the rejection of the instant claim, but relies solely on their rebuttal made for the rejection of the parent claims from which the instantly rejected depend from. Since the arguments had been already rebutted as already discussed above, the rejection is maintained herein.

With regard to Applicants' statement regarding Nerenberg et al. not being a prior art, it is respectfully submitted that Applicants were not granted foreign priority since no certified copy was presented.

Double Patenting - Maintained

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The provisional rejection of claims 1, 2, 4-8, 12-18, 22, 34, 36, and 37 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-21, 25, and 26 of copending Application No. 10/821,568, made in the Office Action mailed on January 7, 2005 is maintained for the reasons of record.

The Rejection:

Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

Independent claim 1 of the instant application and claim 1 of the '568 application are both drawn to a method of detection involving solid-support bound double-stranded DNA and transcriptional factors, wherein said solid-support bound double-stranded DNA are immobilized to the solid support via a spacer of certain length. Claim 1 of the '568 application recites that said spacer comprises a length of about 6.8 nm, while claim 1 of the instant application recites that the length is from about 50 to 250 base pairs, both ranges of which would necessarily overlap.

While the method of signal generation involved in the '568 application is drawn to antibody, the instant invention embraces such detection method as embraced by the generic detection method recited in claim 1 – non radioactive signal.

The transcriptional factors involved in the method of the instant claims and claims of the '568 application are selected from the same Table 1 (see instant claim 7, claim 16 of the '568 application).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments:

Applicants' request to hold the rejection in abeyance until allowable subject matter is identified is noted.

At the present state, the claims are not in condition for allowance, and accordingly, the rejection is maintained for the reasons of record.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is on flex-time schedule and can best be reached from 8:30 a.m. to 4:30 p.m (M-W and F). The Examiner can also be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent

to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Young J. Kim
Primary Examiner
Art Unit 1637
11/13/2006

YOUNG J. KIM
PRIMARY EXAMINER

YJK